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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/090,879	Applicant(s) SOMERS ET AL.
	Examiner David J. Steadman	Art Unit 1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 14 December 2007.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-7 and 30-45 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-7 and 30-45 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on 29 October 2004 is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO/SB/08)
 Paper No(s)/Mail Date 7/29/02

4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____

5) Notice of Informal Patent Application

6) Other: Appendix A

DETAILED ACTION

Status of the Application

[1] The examiner to which this application is assigned in the USPTO has changed.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner David Steadman.

[2] Claims 1-7 and 30-45 are pending in the application.

[3] Applicant's amendment to the claims, filed on 12/14/07, is acknowledged. Claims 8-29 are canceled, claims 1-7 are amended, and claims 30-45 are newly added. This listing of the claims replaces all prior versions and listings of the claims.

Election/Restriction

[4] Applicant's election without traverse of Group I, original claims 1-7, in the response filed on 12/14/07 is acknowledged.

[5] All pending claims are drawn to the elected invention of Group I and are being examined on the merits.

Information Disclosure Statement

[6] The information disclosure statement (IDS) filed on 7/29/02 is acknowledged.

The remarks accompanying the IDS state "All references listed on the enclosed PTO Form 1449 have been previously cited by or submitted to the Office in the prior application, and, in accordance with 37 CFR 1.98(d), copies of these references are not enclosed herewith, but will be provided upon request". Reference E6 has been filed in

the instant application and has been considered as evidenced by the examiner's initials. The examiner has made an earnest attempt to locate the other references as cited in prior application 09/373,432, however, the references appear to have been inadvertently separated from the '432 application file. In order that the cited references may be fully considered, the examiner requests that applicant provide copies of the cited references.

Claim for Domestic Priority

[7] Applicant's claim to domestic priority under 35 U.S.C. 121 to US non-provisional application 09/373,432, filed on 8/13/99, is acknowledged. Applicant's claim to domestic priority under 35 U.S.C. 119(e) to US provisional application 60/096,452, filed on 8/13/98, is acknowledged. The specification amendment filed on 10/16/06 would appear to perfect the priority claim.

[8] Applicant states that this application is a continuation or divisional application of the prior-filed application. A continuation or divisional application cannot include new matter. Applicant is required to change the relationship (continuation or divisional application) to continuation-in-part because this application contains the matter not disclosed in the prior-filed application as described below. See also MPEP 602.05.(a), which states, "[i]f the examiner determines that the continuation or divisional application contains new matter relative to the prior application, the examiner should so notify the applicant in the next Office action. The examiner should also *>(A)< require a new oath

or declaration along with the surcharge set forth in 37 CFR 1.16*>(f)<; and *>(B)< indicate that the application should be redesignated as a continuation-in-part."

Specification/Informalities

[9] The listing of references in the specification at pp. 25-34 is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

[10] The drawing figures filed on 10/29/04 are not properly labeled in accordance with 37 CFR 1.84(u)(1). Appropriate correction is required.

[11] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: ---Crystal of a GDP-Fucose Synthetase Polypeptide---.

[12] The specification is confusing as referring to "Table 1" (p. 21, bottom) and "Table 2" (p. 23, middle) because there does not appear to be a Table 1 and/or 2 filed in the instant application. Appropriate correction is required.

[13] The amendment filed on 10/16/06 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: SEQ ID NO:2 of

the sequence listing filed on 10/16/06. Based on the specification amendment filed on 10/16/06, it appears applicant's intended showing of support for SEQ ID NO:2 is Figure 4, "coli_GFS". However, it is noted that the sequence of SEQ ID NO:2 and that shown in Figure 4, "coli_GFS" appear to be inconsistent as SEQ ID NO:2 appears to have a deletion of Val197 relative to the sequence of "coli_GFS" and is thus not supported by the sequence of Figure 4, "coli_GFS".

Applicant is required to cancel the new matter in the reply to this Office Action. Applicant is further requested to review the sequences of SEQ ID NO:1 and 3 to ensure that they are properly supported by the application as originally filed.

Claim Objection

[14] Claim 7 is objected to in the recitation of "The composition of claim 6" because claim 6 is drawn to "A crystalline complex". In order to substantially improve claim form, it is suggested that the phrase "The composition of claim 6" in claim 7 be amended, for example, to recite "The crystalline complex of claim 6".

[15] Claims 34, 44, and 45 are objected to in the recitation of "diffracts at a resolution" (claim 34) or "diffracts according to the structural coordinates" (claims 44-45) and in order to substantially improve claim form, it is suggested that the noted phrase be amended, for example, to recite "diffracts x-rays at a resolution" (claim 34) or "diffracts x-rays according to the structural coordinates" (claims 44-45).

[16] Claim 35 is objected to in the recitation of "the crystal comprises an active site" because it is the GFS and not the crystal that comprises an active site. In order to

substantially improve claim form, it is suggested that the noted phrase be amended, for example, to recite "the GFS comprises an active site".

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[17] Claim(s) 5-7, 33-34, 36-38, 41, and 44-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 5 is indefinite in the recitation of "mature sequence of naturally-occurring GFS" as it is unclear as to the intended "sequence" and/or form thereof of a naturally-occurring GFS that is considered to be "mature". It is suggested that applicant clarify the scope of sequences that are intended as being encompassed by the claim.

[b] Claim 6 and 7 (claims 39-43 dependent therefrom) are confusing in the recitation of "a second chemical species" as it is unclear as to whether or not the crystalline complex encompasses a first chemical species. It is suggested that applicant clarify the meaning of the claims.

[c] Claims 33, 41, 44, and 45 are confusing in the recitation of "the crystal has diffraction data according to Table 1". Regarding claims 33 and 41, it is noted that a protein crystal would not appear to have any "diffraction data". With respect to claims 33, 41, 44, and 45, the structural coordinate data of Table 1, Table 2, or Protein Data

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Bank entry 1GFS, 1FXS, or 1BSV are a characteristic of the protein and the crystal and while being computer-generated data *from* diffraction data, are not diffraction data *per se*. It is suggested that applicant clarify the meaning of the claims.

[d] Claims 33 and 41 are indefinite in the recitation of "Table 1" and "Table 2" as there does not appear to be a Table 1 and/or 2 filed in the instant application. It is suggested that applicant clarify the meaning of the claims.

[e] Claim 36 is confusing in the recitation of "substitution at Arg36 with Phe40" and it is suggested that applicant clarify the meaning of the noted phrase.

[f] Claim 37 recites the limitation "the active site". There is insufficient antecedent basis for this limitation in the claim, particularly as the GFS of claim 1 is not required to have an active site, nor is it required to have amino acids Ser107, Tyr136, and Lys140. It is suggested that applicant clarify the meaning of the claim.

[g] Claim 38 recites the limitation "Lys140 and Tyr136". There is insufficient antecedent basis for this limitation in the claim, particularly as the GFS of claim 1 is not required to have Tyr136, and Lys140. It is suggested that applicant clarify the meaning of the claim.

[h] Claims 44-45 are indefinite in the recitation of "Protein Databank entry code 1GFS" in claim 44 and "Protein Databank entry code 1FXS or 1BSV" in claim 45. It is well-known in the art that the data represented by a Protein Databank entry code is subject to possible modification and thus is not constant. As such, a skilled artisan would not be apprised of the metes and bounds of the claim by referencing structural coordinates of the respective PDB entry. It is suggested that applicant clarify the

meaning of the claims, *e.g.*, by referring to structural coordinates that are disclosed in the instant application.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[18] Claim(s) 31-34, 36, 38, 40-41, and 43-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163.II.A.3.(b) states, “when filing an amendment an applicant should show support in the original disclosure for new or amended claims” and “[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description”. According to MPEP § 2163.I.B, “While there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure” and “The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that,

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as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc.*, 935 F.2d at 1563-64, 19 USPQ2d at 1117".

Claim 31 recites the limitation "having space group P3₂221 or P3₁21". Claim 32 recites the limitation "the crystal has unit cell parameters of $a=104.2 \text{ \AA}$ and $c=74.9 \text{ \AA}$ ". Claim 33 recites the limitation "the crystal has diffraction data according to Table 1". Claim 34 recites the limitation "The crystalline GFS of claim 1, wherein the crystal diffracts at a resolution of at least 2.2 \AA resolution". Claim 36 recites the limitation "the active site has a substitution at Arg36 with Phe40". Claim 38 recites the limitation "the distance between Lys140 and Tyr136 is at least 4.1 \AA ". Claim 40 recites the limitation "the complex has unit cell parameters of $a=104.2 \text{ \AA}$ and $c=75.1 \text{ \AA}$ ". Claim 41 recites the limitation "the crystal has diffraction data according to Table 2". Claim 43 recites the limitation "the complex has unit cell parameters of $a=104.3 \text{ \AA}$ and $c=74.9 \text{ \AA}$ ". Claim 44 recites the limitation "the crystal diffracts according to...Protein Databank entry code 1GFS". Claim 45 recites the limitation "the crystal complex diffracts according to...Protein Databank entry code 1FXS or 1BSV".

Regarding the limitations of claims 31-34 and 44, the specification discloses a working example of crystalline *E. coli* GFS having unit cell parameters $a=104.2 \text{ \AA}$ and $c=74.9 \text{ \AA}$ and space group symmetry P3₂221 or P3₁21 (p. 21) deposited as PDB entry 1GFS (p. 24, middle). This disclosure of a specific species of crystal would not appear to support a genus of any GFS crystal *from any source* having the recited unit cell parameters, space group symmetries, and structural coordinates. See particularly MPEP 2163.05.I and 2163.05.III.

Regarding the claim 36 limitation, the examiner can find no mention of a substitution of Arg36 with Phe40 in the instant specification.

Regarding the claim 38 limitation, it is noted the specification discloses, "In the GFS structure we find the distance between NC of Lys140 and the hydroxyl of Tyr136 (4.1 Å) is too far to stabilize the negative charge on the tyrosine hydroxyl by hydrogen bond interaction". This disclosure would not appear to support a crystal of GFS from *any* source wherein Lys140 and Tyr136 have a distance of *at least* 4.1 Å. See particularly MPEP 2163.05.I and 2163.05.III.

Regarding the limitations of claims 40-41, 43, and 45 the specification discloses a working example of crystalline *E. coli* GFS in complex with NADP+ having unit cell parameters a=104.2 Å and c=75.1 Å, wherein the *E. coli* GFS-NADP+ complex has structural coordinates of Table 2 (paragraph bridging pp. 23-24) deposited as PDB entry 1FXS (p. 24, middle) and a working example crystalline *E. coli* GFS in complex with NADPH having unit cell parameters a=104.3 Å and c=74.9 Å (p. 24, top) deposited as PDB entry 1BSV (p. 24, middle). This disclosure of specific species of crystals would not appear to support a genus of GFS crystals *from any source* having the recited unit cell parameters, space group symmetries, and structural coordinates. See particularly MPEP 2163.05.I and 2163.05.III.

It is suggested that applicant show support for the limitations at issue.

[19] Claim(s) 1-7 and 30-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)."

The claims are drawn to a crystalline GDP-fucose synthetase ("GFS") polypeptide from any source having any sequence of amino acids, alone or in complex with any ligand.

MPEP 2163.II.A.2.(a).i) states, "Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention".

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a

representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 further states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In general, for a genus of crystals to be adequately described, the following must be adequately disclosed: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, including the protein and any molecule(s) bound to it, (2) the space group, and (3) the unit cell dimensions of the crystal.

In this case, the specification discloses only three representative species of the genus of GFS crystals, *i.e.*, 1) crystalline *E. coli* GFS of SEQ ID NO:2 having unit cell parameters $a=104.2\text{ \AA}$ and $c=74.9\text{ \AA}$ and space group symmetry $P3_221$ or $P3_121$ (p. 21); 2) crystalline *E. coli* GFS of SEQ ID NO:2 in complex with NADP+ having unit cell parameters $a=104.2\text{ \AA}$ and $c=75.1\text{ \AA}$ with an undefined space group symmetry; and 3) crystalline *E. coli* GFS of SEQ ID NO:2 in complex with NADPH having unit cell parameters $a=104.3\text{ \AA}$ and $c=74.9\text{ \AA}$ with an undefined space group symmetry.

The specification fails to describe any additional representative species of the recited genus of crystalline forms, which encompasses widely variant species, including

crystals of any GFS polypeptide from any source having any sequence of amino acids, optionally in complex with any ligand, having any space group and unit cell dimensions. As such, it appears the genus encompasses widely variant species. In this case, the art of protein crystallization is highly unpredictable as evidenced by the reference of McPherson et al. (*Eur. J. Biochem.* 189:1-23, 1990), which states (p. 13, column 2), "Table 2 lists physical, chemical and biological variables that may influence to a greater or less extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids." Table 2 is a list of 25 different variables that can or do affect protein crystallization. As McPherson points out trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by even a single amino acid can result in significant influences upon the change in which variables are important for successful crystallization. McPherson also goes on to teach, "[b]ecause each protein is unique, there are few means available to predict in advance the specific values of a variable, or sets of conditions that might be most profitably explored. Finally, the various parameters under one's control are not independent of one another and their interrelations may be complex and difficult to discern. It is therefore, not easy to elaborate rational guidelines relating to physical factors or ingredients in the mother liquor that can increase the probability of success in crystallizing a particular protein. The specific component and condition must be carefully deduced and refined for each

individual." Applicant's own specification appears to corroborate the teachings of McPherson by disclosing that "Attempts to soak the GDP-4-keto, 6-deoxy mannose substrate or GDP into the crystals failed" (p. 15, top). Thus, in view of these teachings, a skilled artisan would recognize there is a high level of unpredictability in making a protein crystal.

While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." Accordingly, given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[20] Claims 1-7 and 30-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: 1) crystalline *E. coli* GFS of SEQ ID NO:2 having unit cell parameters $a=104.2\text{ \AA}$ and $c=74.9\text{ \AA}$ and space group symmetry $P3_2221$ or $P3_121$ (p. 21); 2) crystalline *E. coli* GFS of SEQ ID NO:2 in complex with NADP+ having unit cell parameters $a=104.2\text{ \AA}$ and $c=75.1\text{ \AA}$; and 3) crystalline *E. coli* GFS of SEQ ID NO:2 in complex with NADPH having unit cell parameters $a=104.3\text{ \AA}$ and $c=74.9\text{ \AA}$, does not reasonably provide enablement for all GFS crystals as broadly encompassed by the claims. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

"The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims...and explicitly set forth the scope of the claim when writing an Office action." Also, MPEP 2164.08 states, "[a]ll questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims...claims are to be given their broadest reasonable interpretation that is consistent with the specification."

The claims are drawn to a crystalline GDP-fucose synthetase ("GFS") polypeptide from any source having any sequence of amino acids, alone or in complex with any ligand. The broad scope of claimed crystals is not commensurate with the enablement provided by the disclosure. In this case the disclosure is limited to 1) crystalline *E. coli* GFS of SEQ ID NO:2 having unit cell parameters $a=104.2\text{ \AA}$ and $c=74.9\text{ \AA}$ and space group symmetry P3₂221 or P3₁21 (p. 21); 2) crystalline *E. coli* GFS of SEQ ID NO:2 in complex with NADP⁺ having unit cell parameters $a=104.2\text{ \AA}$ and $c=75.1\text{ \AA}$; and 3) crystalline *E. coli* GFS of SEQ ID NO:2 in complex with NADPH having unit cell parameters $a=104.3\text{ \AA}$ and $c=74.9\text{ \AA}$.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: Even though a crystal of *E. coli* GDP-fucose synthetase was known in the art at the time of the invention (see Tonetti et al., *Acta Crystallogr D Biol Crystallogr* 54:684-687, July 1998), the state of the art at the time of the invention acknowledges a high level of unpredictability for making a protein crystal. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "The first prerequisite for solving the three-dimensional structure of a protein by x-ray crystallography is a well-ordered crystal that will diffract x-rays strongly...[w]ell-ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth et al. ("Principles of

X-ray Crystallography," Springer, New York, 1999) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). Also, Wiencek (*Ann Rev Biomed Eng* 1:505-534) teaches that "[p]rotein solubility will change dramatically as pH is altered by ~ 0.5 pH units...some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). See also the teachings of McPherson et al. (*supra*).

Additionally, Buts et al. (*Acta Cryst D61:1149-1159, 2005*) teaches that "Since the introduction of structural genomics, the protein has been recognized as the most important variable in crystallization." "Five naturally occurring variants, differing in 1-18 amino acids, of the 177-residue lectin domain of the F17G fimbrial adhesin were expressed and purified in identical ways. For four out of the five variants crystals were obtained, mostly in non-isomorphous space groups, with diffraction limits ranging between 2.4 and 1.1 Å resolution." Specifically, the reference of Buts et al. teaches that the F17e-G and F17f-G adhesins differ in only one amino acid from the F17c-G adhesin, Arg21Ser and His36Tyr, respectively, and yet these proteins that are 99%

identical in sequence resulted in different crystal forms with distinct diffraction properties (see Tables 1-3).

Skarzynski et al. (Acta Cryst D62:102-107, 2006) teaches "crystals of complexes obtained by compound soaking may become damaged, change their diffraction properties or even change the space group during the soaking experiment!" (p. 103, right column, middle). Skarzynski et al. further teaches that binding of potent compounds during soaking often causes complete or partial disruption of the crystal lattice, poorly soluble compounds may interfere with the diffraction pattern of the protein crystal sample, and very often no binding is observed for active compounds, despite their potency under biochemical or biological assay conditions" (p. 104, left column, middle). The teachings of Skarzynski et al. are supported by applicant's specification, which teaches "Attempts to soak the GDP-4-keto, 6-deoxy mannose substrate or GDP into the crystals failed" (p. 15, top).

Even though the skill in the art is extremely high, even for those that are graced by being assisted with the latest technologies such as automated robotics, the art of crystallography is still rooted in trial-and-error procedures (see Abstract, Kundrot et al. Cell. Mol. Life Sci. 2004, 61: 525-536) and currently there are no directed methods which makes this process any easier or more predictable. Thus, each protein that is to be crystallized needs to be treated as its own entity possessing its own unique biochemical crystallization parameters which cannot be inferred or learned from other crystallized proteins.

The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily work for a protein complex and vice-versa which may even contain the same protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein) complex (see also Weber, Methods in Enzymology, 1997, Vol. 276, pp. 13-22). At best, the art of crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful. Even then, there is no guarantee. It is even a well known fact in the art that luck often times play a role in obtaining crystallization conditions despite the extremely high skill level of those in the art (see Drenth, *supra* and Cudney, Rigaku Journal, 1999, Vol. 16, No. 1, pp. 1-7).

Thus, in view of these teachings, a skilled artisan would recognize there is a high level of unpredictability in making a protein crystal.

The amount of direction provided by the inventor; The existence of working examples: As noted above, the specification discloses three working examples of GFS crystals, *i.e.*, 1) crystalline *E. coli* GFS of SEQ ID NO:2 having unit cell parameters $a=104.2\text{ \AA}$ and $c=74.9\text{ \AA}$ and space group symmetry P3₂221 or P3;21 (p. 21); 2) crystalline *E. coli* GFS of SEQ ID NO:2 in complex with NADP⁺ having unit cell parameters $a=104.2\text{ \AA}$ and $c=75.1\text{ \AA}$; and 3) crystalline *E. coli* GFS of SEQ ID NO:2 in

complex with NADPH having unit cell parameters $a=104.3\text{ \AA}$ and $c=74.9\text{ \AA}$. However, since the specification fails to provide the necessary guidance for crystallizing all other GFS polypeptides as encompassed by the claims.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallography were known at the time of the invention, it was not routine in the art to screen all polypeptides, in apo-form or complexed with any ligand as encompassed by the claims for those that will yield diffraction-quality crystals.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all crystals and polypeptides as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims Rejections – 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[21] Claims 1-3, 5, 35, and 37 are rejected under 35 U.S.C. 102(a) as being anticipated by Tonetti et al. (*Acta Crystallogr D Biol Crystallog* 54:684-687, July 1998; "Tonetti"). The claims are drawn to a crystalline GFS polypeptide.

The reference of Tonetti teaches a crystal of recombinant GDP-4-keto-6-deoxy-D-mannose epimerase/reductase from *E. coli* having space group P3₁21 (p. 685, column 2, under *Results and Discussion*). Tonetti teaches the GDP-4-keto-6-deoxy-D-mannose epimerase/reductase, which is interpreted herein as being a GDP-fucose synthetase as noted above, has the amino acids as recited in claims 35 and 37 (p. 684, Figure 1). This anticipates claims 1-3, 5, 35, and 37 as written.

EXAMINER CLARIFICATION: It is noted that the enzyme of the crystal of Tonetti is described as a GDP-4-keto-6-deoxy-D-mannose epimerase/reductase and not a GDP-fucose synthetase. However, the sequence of the GDP-4-keto-6-deoxy-D-mannose epimerase/reductase of Tonetti as shown in Figure 1 would appear to be

identical to the amino acid sequence of an *E. coli* GDP-fucose synthetase (see Appendix A). Also, the instant specification appears to acknowledge that GDP-fucose synthetase is alternatively referred to as the enzyme of Tonetti (p. 6, middle). Moreover, Tonetti discloses the GDP-4-keto-6-deoxy-D-mannose epimerase/reductase was able to convert substrate to GDP-fucose. As such, the enzyme of Tonetti is an *E. coli* GDP-fucose synthetase.

[22] Claim 31 is rejected under 35 U.S.C. 102(b) as being anticipated by Tonetti (*supra*). Claim 31 limits the crystal of claim 1 to having space group P3₂1 or P3₁21.

Tonetti teaches the GDP-4-keto-6-deoxy-D-mannose epimerase/reductase crystal, which is interpreted herein as a GFS crystal as noted above, has space group P3₁21 (p. 685, column 2, middle). This anticipates claim 31 as written.

EXAMINER CLARIFICATION: As noted above, descriptive support for the limitations of claim 31 cannot be found in the earlier-filed applications. It is noted that the instant rejection is made under 35 U.S.C. 102(b) based upon a priority date of 3/4/02 for claim 31.

[23] Claim 38 is rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as being obvious over Tonetti (*supra*). Claim 38 limits the GFS of the crystal of claim 1 to having a Lys140 and a Tyr136, with a distance between the Lys140 and Tyr136 of at least 4.1 Å.

The teachings of Tonetti are set forth above. It is acknowledged that Tonetti does not expressly teach the GDP-4-keto-6-deoxy-D-mannose epimerase/reductase, which is interpreted herein as a GFS, of the crystal has a distance between Lys140 and Tyr136 of at least 4.1 Å. However, since the sequence of the GFS of Tonetti: 1) appears to be the same as that of the *E. coli* GFS crystal disclosed herein, 2) has the same space group as the disclosed crystal, and 3) has unit cell parameters that nearly identical to the crystal disclosed herein, it is the examiner's position that the Lys140 and Tyr136 of the GFS of the crystal of Tonetti would have a distance of at least 4.1 Å.

Since the Office does not have the facilities for examining and comparing applicant's crystal with the crystal of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

[24] Claims 31-34, 38, 40-41, and 43-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Somers et al. (*Structure* 6:1601-1612, December 1998; "Somers"). The claims are drawn to crystalline GFS having the limitations as recited therein.

Somers teaches a crystal of native *E. coli* GDP-fucose synthetase having space group P3₂1 or P3₁21 with unit cell parameters of $a = 104.2 \text{ \AA}$ and $c = 74.9 \text{ \AA}$ (p. 1609, column 1, middle) that diffracts x-rays to a resolution of 2.2 Å (p. 1609, Table 1, under *Native*), discloses as having a 4.1 Å distance between Tyr136 and Lys140 (p. 1607, column 2, middle). Somers further teaches a crystal of *E. coli* GDP-fucose synthetase in complex with NADP⁺ with unit cell parameters of $a = 104.2 \text{ \AA}$ and $c = 75.1 \text{ \AA}$ (p. 1609,

column 2, middle) and a crystal of *E. coli* GDP-fucose synthetase in complex with NADPH with unit cell parameters of $a = 104.3 \text{ \AA}$ and $c = 74.9 \text{ \AA}$ (p. 1619, paragraph bridging columns 1-2). According to Somers, the structural coordinates for the GDP-fucose synthetase polypeptides have PDB entry accession codes 1GFS, 1FXS, and 1BSV (p. 1610, column 2, bottom). This anticipates claims 31-34, 38, 40-41, and 43-45 as written.

EXAMINER CLARIFICATION: As noted above, descriptive support for the limitations of claims 31-34, 38, 40-41, and 43-45 cannot be found in the earlier-filed applications. It is noted that the instant rejection is made under 35 U.S.C. 102(b) based upon a priority date of 3/4/02 for the rejected claims.

Examiner Comment/Clarification

[25] It is noted that if applicant replaces the sequence of SEQ ID NO:2 with that shown in Figure 4, "coli_GFS", the rejections under 35 U.S.C. 102 above may apply to instant claim 30.

Conclusion

[26] Status of the claims:

Claims 1-7 and 30-45 are pending.

Claims 1-7 and 30-45 are rejected.

No claim is in condition for allowance.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Steadman/
David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656

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APPENDIX A

PCL_ECOLI

ID PCL_ECOLI Reviewed; 321 AA.

AC P32055; P76382;

DT 01-OCT-1993, integrated into UniProtKB/Swiss-Prot.

DT 01-NOV-1997, sequence version 2.

DT 24-JUL-2007, entry version 65.

DE GDP-L-fucose synthetase (EC 1.1.1.271) (GDP-4-keto-6-deoxy-D-mannose-3,5-epimerase-4-reductase).

GN Name=fcl; Synonyms=wcaG; OrderedLocusNames=b2052, JW2037;

GS Escherichia coli.

OC Bacteria; Proteobacteria; Gammaproteobacteria; Enterobacteriales;

OC Enterobacteriaceae; Escherichia.

OX NCBI_TaxID=562;

RN [1]

RP NUCLEOTIDE SEQUENCE [GENOMIC DNA].

RC STRAIN=K12;

RX MEDLINE=95115532; PubMed=7815923;

RA Aoyama K., Haase A.M., Reeves P.R.;

RT "Evidence for effect of random genetic drift on G+C content after lateral transfer of fucose pathway genes to *Escherichia coli* K-12.";

RL Mol. Biol. Evol. 11:829-838 (1994).

RN [2]

RP NUCLEOTIDE SEQUENCE [GENOMIC DNA].

RC STRAIN=K12;

RX MEDLINE=96326333; PubMed=8759852;

RA Stevenson G., Andrianopoulos K., Hobbs M., Reeves P.R.;

RT "Organization of the *Escherichia coli* K-12 gene cluster responsible for production of the extracellular polysaccharide colanic acid.";

RL J. Bacteriol. 178:4885-4893 (1996).

RN [3]

RP NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].

RC STRAIN=K12 / W3110 / ATCC 27325 / DSM 5911;

RX MEDLINE=97251358; PubMed=9097040; DOI=10.1093/dnare/3.6.379;

RA Itoh T., Aiba H., Baba T., Fujita K., Hayashi K., Inada T., Isono K., Kasai H., Kimura S., Kitakawa M., Kitagawa M., Makino K., Miki T., Mizobuchi K., Mori H., Mori T., Motomura K., Nakade S., Nakamura Y., Nishimoto H., Nishio Y., Oshima T., Saito N., Sampei G., Seki Y., Sivasundaram S., Tagami H., Takeda J., Takemoto K., Wada C., Yamamoto Y., Horiuchi T.;

RT "A 460-kb DNA sequence of the *Escherichia coli* K-12 genome corresponding to the 40.1-50.0 min region on the linkage map.";

RL DNA Res. 3:379-392 (1996).

RN [4]

RP NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].

RC STRAIN=K12 / MG1655 / ATCC 47076;

RX MEDLINE=972512617; PubMed=9097053; DOI=10.1126/science.277.5331.1453;

RA Blattner F.R., Plunkett G. III, Bloch C.A., Perna N.T., Burland V., Riley M., Collado-Vides J., Glasner J.D., Rode C.K., Mayhew G.F., Gregor J., Davis N.W., Kirkpatrick H.A., Goeden M.A., Rose D.J., Mau B., Shao Y.;

RT "The complete genome sequence of *Escherichia coli* K-12.";

RL Science 277:1453-1474 (1997).

RN [5]

RP NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].

RC STRAIN=K12 / W3110 / ATCC 27325 / DSM 5911;

RX PubMed=16738553; DOI=10.1038/msb4100049;

RA Hayashi K., Morooka N., Yamamoto Y., Fujita K., Isono K., Choi S., Ohtsubo E., Baba T., Wanner B.L., Mori H., Horiuchi T.;

RT "Highly accurate genome sequences of *Escherichia coli* K-12 strains MG1655 and W3110.";

RL Mol. Syst. Biol. 2:E1-E5 (2006).

RN [6]

RP CHARACTERIZATION.

RX MEDLINE=98132401; PubMed=9473059;

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RA Andrianopoulos K., Wang L., Reeves P.R.;
 RT "Identification of the fucose synthetase gene in the colanic acid gene
 RT cluster of Escherichia coli K-12.";
 RL J. Bacteriol. 180:998-1001(1998).
 RN [7]
 RP X-RAY CRYSTALLOGRAPHY (2.2 ANGSTROMS).
 RC STRAIN=K12;
 RX MEDLINE=99081889; PubMed=9862812; DOI=10.1016/S0969-2126(98)00157-9;
 RA Somers W.S., Stahl M.L., Sullivan F.X.;
 RT "GDP-fucose synthetase from Escherichia coli: structure of a unique
 RT member of the short-chain dehydrogenase/reductase family that
 RT catalyzes two distinct reactions at the same active site.";
 RL Structure 6:1601-1612(1998).
 CC !- FUNCTION: Two step NADP-dependent conversion of GDP-4-dehydro-6-
 CC deoxy-D-mannose to GDP-fucose, involving an epimerase and a
 CC reductase reaction.
 CC !- CATALYTIC ACTIVITY: GDP-L-fucose + NADP(+) = GDP-4-dehydro-6-
 CC deoxy-D-mannose + NADPH.
 CC !- PATHWAY: Carbohydrate biosynthesis: GDP-L-fucose biosynthesis via
 CC de novo pathway; GDP-L-fucose from GDP-D-mannose: step 2/2.
 CC !- PATHWAY: Context: Polysaccharide colanic acid biosynthesis.
 CC !- SUBUNIT: Homodimer.
 CC !- SUBCELLULAR LOCATION: Cytoplasm.
 CC !- SIMILARITY: Belongs to the fucose synthetase family.
 CC -----
 CC Copyrighted by the UniProt Consortium, see <http://www.uniprot.org/terms>
 CC Distributed under the Creative Commons Attribution-NoDerivs License
 CC -----
 DR EMBL; U38473; AAC77843.1; -; Genomic_DNA.
 DR EMBL; U00096; AAC75113.1; -; Genomic_DNA.
 DR EMBL; AP009046; BAA15908.1; -; Genomic_DNA.
 DR PIR; C64971; C64971.
 DR PDB; 1BSV; X-ray; A=1-321.
 DR PDB; 1BSW; X-ray; A=1-321.
 DR PDB; 1E6U; X-ray; A=1-321.
 DR PDB; 1E7Q; X-ray; A=1-321.
 DR PDB; 1E7R; X-ray; A=1-321.
 DR PDB; 1E7S; X-ray; A=1-321.
 DR PDB; 1FXS; X-ray; A=1-321.
 DR PDB; 1GFS; X-ray; A=1-321.
 DR IntAct; P32055; -.
 DR GenomeReviews; U00096_GR; b2052.
 DR GenomeReviews; AP009046_GR; JW2037.
 DR KEGG; ec012037; -.
 DR KEGG; ec01b2052; -.
 DR EchoBASE; EB1736; -.
 DR EcoGene; EG11788; fc1.
 DR BioCyc; EcoCyc;FC1-MONOMER; -.
 DR LinkHub; F32055; -.
 DR GO; GO:0050577; F:GDP-L-fucose synthase activity; IEA:EC.
 DR InterPro; IPR001509; Epimerase_Dh.
 DR Pfam; PF01370; Epimerase; 1.
 PE 1: Evidence at protein level;
 KW 3D-structure; Complete proteome; Cytoplasm; Isomerase;
 KW Lipopolysaccharide biosynthesis; Multifunctional enzyme; NADP;
 KW Oxidoreductase.
 FT CHAIN 1 321 GDP-L-fucose synthetase.
 FT FTID=PRO_0000174358.
 FT CONFLICT 255 256 EL -> DV (in Ref. 1 and 2).
 FT STRAND 4 9
 FT TURN 10 12
 FT HELIX 14 23
 FT STRAND 29 32
 FT TURN 36 38
 FT HELIX 44 54
 FT STRAND 57 61
 FT HELIX 69 74

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FT HELIX 76 96
 FT STRAND 101 105
 FT HELIX 108 110
 FT STRAND 117 119
 FT HELIX 121 123
 FT HELIX 131 133
 FT HELIX 134 154
 FT STRAND 157 163
 FT STRAND 165 168
 FT HELIX 180 194
 FT STRAND 197 203
 FT STRAND 211 213
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 FT STRAND 243 246
 FT HELIX 253 264
 FT STRAND 268 273
 FT HELIX 288 292
 FT HELIX 301 314
 SQ SEQUENCE 321 AA; 36141 MW; 97077193D79684C7 CRC64;

Query Match 99.4%; Score 1646.5; DB 1; Length 321;
 Best Local Similarity 99.7%; Pred. No. 3.6e-120;
 Matches 316; Conservative 0; Mismatches 0; Indels 1; Gaps 1;

Qy 1 KQRVFIAGHRGMVGSAIRRQLEQRGDVEVLRLTRDELNLLDSRAVHDFFASERIDQVYLA 60
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 Db 3 KQRVFIAGHRGMVGSAIRRQLEQRGDVEVLRLTRDELNLLDSRAVHDFFASERIDQVYLA 62

Qy 61 AAKVGGIVANNTYPADPIYQNMIESNIHAAHQNDVNKLFLGSSCIYPKLAKQPMAES 120
 |||||||
 Db 63 AAKVGGIVANNTYPADPIYQNMIESNIHAAHQNDVNKLFLGSSCIYPKLAKQPMAES 122

Qy 121 ELLQGTLLEPTNEPYIAKIAKIGIKLCESYNRQYGRDYRSVMPNTLYGPHDNFPNSNSHVIP 180
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 Db 123 ELLQGTLLEPTNEPYIAKIAKIGIKLCESYNRQYGRDYRSVMPNTLYGPHDNFPNSNSHVIP 182

Qy 181 ALLRRPHEATAQNAPD-VVWGSCTPMREFLHVDDMAAASIHVMLAHEVWLNTQPMLSH 239
 |||||||
 Db 183 ALLRRPHEATAQNAPDVVWGSCTPMREFLHVDDMAAASIHVMLAHEVWLNTQPMLSH 242

Qy 240 INVGTGVDCITIRELAQTIAKVVGYKGRVVFASKPDGTPRKLLDVTRLHQLGWYHEISLE 299
 |||||||
 Db 243 INVGTGVDCITIRELAQTIAKVVGYKGRVVFASKPDGTPRKLLDVTRLHQLGWYHEISLE 302

Qy 300 AGLASTYQWFLENQDRF 316
 |||||||
 Db 303 AGLASTYQWFLENQDRF 319